

09/821,416

=> d his

(FILE 'HOME' ENTERED AT 21:37:18 ON 23 JAN 2003)

FILE 'CAPLUS' ENTERED AT 21:37:27 ON 23 JAN 2003

L1 10 S MGLUR5(P) (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? O

FILE 'REGISTRY' ENTERED AT 21:40:14 ON 23 JAN 2003

L2 STRUCTURE UPLOADED

FILE 'STNGUIDE' ENTERED AT 21:40:55 ON 23 JAN 2003

FILE 'REGISTRY' ENTERED AT 21:42:48 ON 23 JAN 2003

L3 STRUCTURE UPLOADED

L4 2 S L3 SSS SAM

L5 17 S L3 SSS FULL

FILE 'CAPLUS' ENTERED AT 21:43:36 ON 23 JAN 2003

L6 14 S L5

L7 0 S L6 AND (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? OR

L8 0 S L6 AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)

FILE 'STNGUIDE' ENTERED AT 21:45:33 ON 23 JAN 2003

FILE 'REGISTRY' ENTERED AT 21:46:54 ON 23 JAN 2003

L9 STRUCTURE UPLOADED

L10 50 S L9 SSS SAM

L11 2061 S L9 SSS FULL

FILE 'CAPLUS' ENTERED AT 21:47:23 ON 23 JAN 2003

=> s l11 and (anxiety or anxious? or anxioly?)

1052 L11

9325 ANXIETY

395 ANXIOUS?

7715 ANXIOLY?

L12 19 L11 AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)

=> s l12 and mglur5(p) (antagonist? or inhibit?)

460 MGLUR5

189529 ANTAGONIST?

1540801 INHIBIT?

196 MGLUR5(P) (ANTAGONIST? OR INHIBIT?)

L13 2 L12 AND MGLUR5(P) (ANTAGONIST? OR INHIBIT?)

09/821,416

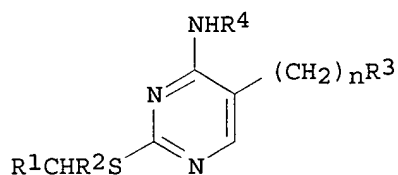
=> s mglur5(p) (inhibit? or antagonist?) and (anxiety or anxious? or anxioly?)

460 MGLUR5  
1540801 INHIBIT?  
189529 ANTAGONIST?  
196 MGLUR5(P) (INHIBIT? OR ANTAGONIST?)  
9325 ANXIETY  
395 ANXIOUS?  
7715 ANXIOLY?

L1 10 MGLUR5(P) (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)

=> d l1 abs ibib kwic 1-10

L1 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS  
GI



I

AB 4-Aminopyrimidines I [R<sup>1</sup> = (un)substituted alkenyl, alkynyl, cycloalkyl, heteroaryl, alkoxy carbonyl, alkenyloxy carbonyl, alkynyloxy carbonyl, cycloalkoxy carbonyl, cycloalkylmethoxy carbonyl, heteroarylmethoxy carbonyl; R, R<sup>4</sup> = H, alkyl; R<sup>3</sup> = (un)substituted aryl, heteroaryl, alkoxy carbonyl; n = 0-2] were prep'd. for use in the prevention or treatment of mGluR5 receptor mediated disorders. Thus, PhNHCH<sub>2</sub>CH<sub>2</sub>Cn was treated with PhCHO and the resulting acrylonitrile was cyclized with urea and treated with BrCH<sub>2</sub>CO<sub>2</sub>Et to give I [R<sup>1</sup> = CO<sub>2</sub>Et, R<sup>2</sup>, R<sup>4</sup> = H, R<sup>3</sup> = Ph, n = 1] which had glutamate antagonist IC<sub>50</sub> on rat mGlu 5a receptors of 0.14 .mu.M.

ACCESSION NUMBER: 2002:906173 CAPLUS  
DOCUMENT NUMBER: 137:384860  
TITLE: 4-Aminopyrimidines for treatment of mGluR5 receptor mediated disorders  
INVENTOR(S): Mutel, Vincent; Peters, Jens-uwe; Wichmann, Juergen  
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.  
SOURCE: PCT Int. Appl., 32 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|--|------|----------|-----------------|----------|
| WO 2002094795  | A1   | 20021128 | WO 2002-EP5379  | 20020516 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, |      |          |                 |          |

09/821,416

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,  
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2001-112564 A 20010523

OTHER SOURCE(S): MARPAT 137:384860

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB 4-Aminopyrimidines I [R1 = (un)substituted alkenyl, alkynyl, cycloalkyl,  
heteroaryl, alkoxy carbonyl, alkenyloxy carbonyl, alkynyloxy carbonyl,  
cycloalkoxy carbonyl, cycloalkylmethoxy carbonyl, heteroarylmethoxy carbonyl;  
R, R4 = H, alkyl; R3 = (un)substituted aryl, heteroaryl, alkoxy carbonyl; n  
= 0-2] were prepd. for use in the prevention or treatment of  
mGluR5 receptor mediated disorders. Thus, PhNhCH2CH2Cn was  
treated with PhCHO and the resulting acrylonitrile was cyclized with urea  
and treated with BrCH2CO2Et to give I [R1 = CO2Et, R2, R4 = H, R3 = Ph, n  
= 1] which had glutamate **antagonist** IC50 on rat mGlu 5a  
receptors of 0.14 .mu.M.

IT Analgesics

Anxiety

Anxiolytics

Glutamate **antagonists**

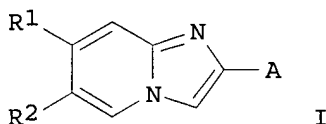
Human

Pain

(prepn. of 4-aminopyrimidines for treatment of mGluR5  
receptor mediated disorders)

L1 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS

GI



AB The title compds. [I; R1, R2 = H, alkyl, halogen, OH, alkoxy; A =  
(un)substituted aryl, heteroaryl, etc.], useful for the manuf. of  
medicaments for the treatment or prevention of GluR5 receptor mediated  
disorders, such as acute and/or chronic neurol. disorders, were prepd. and  
formulated. Thus, reacting 2-amino-4-chloropyridine with  
3,4-dimethylphenacyl bromide in EtOH afforded 69% 7-chloro-2-(3,4-  
dimethylphenyl)imidazo[1,2-a]pyridine which showed IC50 of 0.1 .mu.M  
against mGluR 5a receptor binding.

ACCESSION NUMBER: 2002:888557 CAPLUS

DOCUMENT NUMBER: 137:384841

TITLE: Preparation of imidazo[1,2-a]pyridines as  
**mGluR5 antagonists**

INVENTOR(S): Mutel, Vincent; Peters, Jens-Uwe; Wichmann, Juergen

PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

Delacroix

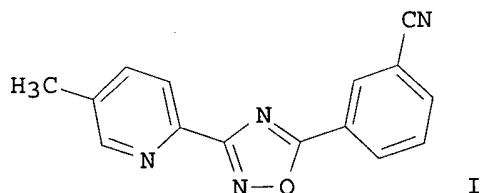
09/821,416

PATENT INFORMATION:

| PATENT NO.  | KIND  | DATE   | APPLICATION NO. | DATE     |
|---|---|--|-----------------|----------|
| WO 2002092086   | A1  | 20021121   | WO 2002-EP3098  | 20020320 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |   |  |                 |          |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  |   |  |                 |          |
| US 2002188128   | A1  | 20021212   | US 2002-93790   | 20020308 |
| PRIORITY APPLN. INFO.:  |   | EP 2001-107562 A 20010327  |                 |          |
| OTHER SOURCE(S):  |   | MARPAT 137:384841  |                 |          |
| REFERENCE COUNT:  |   | 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT |                 |          |
| TI  | Preparation of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b>   |  |                 |          |
| ST  | imidazopyridine prepn metabotropic glutamate 5 receptor <b>mGluR5 antagonist</b> analgesic  |  |                 |          |
| IT  | Nervous system<br>(Huntington's chorea, treatment of; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )  |  |                 |          |
| IT  | Nervous system<br>(amyotrophic lateral sclerosis, treatment of; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )  |  |                 |          |
| IT  | Mental disorder<br>(cognitive, treatment of; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )   |  |                 |          |
| IT  | Mental disorder<br>(depression, treatment of; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )  |  |                 |          |
| IT  | Nervous system<br>(disease, treatment of; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )  |  |                 |          |
| IT  | Cognition<br>(disorder, treatment of; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )  |  |                 |          |
| IT  | Glutamate receptors<br>RL: BSU (Biological study, unclassified); BIOL (Biological study)<br>(metabotropic, <b>mGluR5</b> ; prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> )   |  |                 |          |
| IT  | Analgesics<br>Anti-Alzheimer's agents<br>Anti-ischemic agents<br>Anticonvulsants<br>Antiparkinsonian agents<br>Antipsychotics<br><b>Anxiolytics</b><br>Cognition enhancers<br>Human<br>Nervous system agents<br>(prepn. of imidazo[1,2-a]pyridines as <b>mGluR5 antagonists</b> ) |  |                 |          |
| IT  | Mental disorder   |  |                 |          |

Delacroix

- (psychosis, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)
- IT Memory, biological  
(retention defect, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)
- IT Mental disorder  
(senile psychosis, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)
- IT Alzheimer's disease  
**Anxiety**  
Epilepsy  
Ischemia  
Multiple sclerosis  
Pain  
Parkinson's disease  
Schizophrenia  
(treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)
- IT 885-91-6P 34658-67-8P 65964-60-5P 88965-00-8P 100965-76-2P  
158959-20-7P 205655-15-8P 326018-20-6P 419557-33-8P 420832-11-7P  
475992-33-7P 475992-34-8P 475992-35-9P 475992-36-0P 475992-37-1P  
475992-38-2P 475992-39-3P 475992-40-6P 475992-41-7P 475992-42-8P  
475992-43-9P 475992-44-0P 475992-45-1P 475992-46-2P 475992-47-3P  
475992-48-4P 475992-49-5P 475992-50-8P 475992-51-9P  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)  
(prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)
- IT 504-29-0, 2-Aminopyridine 695-34-1, 2-Amino-4-methylpyridine 1603-41-4  
1835-02-5, 3,4-Dimethoxyphenacyl bromide 1835-12-7 2003-10-3  
2227-64-7 2633-50-3, 3,4-Dimethylphenacyl bromide 4629-54-3  
5000-65-7 10201-73-7, 2-Amino-4-methoxypyridine 10531-42-7  
18523-22-3 19798-80-2, 2-Amino-4-chloropyridine 23489-36-3  
26167-45-3 33252-32-3 39696-16-7 41011-01-2 51012-64-7  
53631-18-8 61858-38-6 122654-17-5 151427-19-9 435273-49-7  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)
- L1 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS  
GI



- AB The invention provides compds. and pharmaceutical compns. that act as **antagonists** at metabotropic glutamate receptors, and that are

useful for treating neurol. diseases and disorders. Methods of prepg. the compds. also are disclosed. The compds. exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, notably **mGluR5**. In particular, medical conditions assocd. with metabotropic glutamate receptors and therefore targeted by the invention compds. include stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease. The invention provides methods of treating diseases assocd. with excitatory activation of an mGluR Group I receptor, and of **inhibiting** neuronal damage caused by excitatory activation of an mGluR Group I receptor, specifically wherein the mGluR Group I receptor is **mGluR5**. In one aspect of the invention, the **antagonists** may be represented by the general formula Ar1-L-Ar2, wherein Ar1 is an optionally substituted heteroarom. moiety, and Ar2 is an optionally substituted benzene ring. The L moiety is a group that not only covalently binds to the Ar1 and Ar2 moieties, and which facilitates adoption of the correct spatial orientation of Ar1 and Ar2, but also itself may interact with the protein, to effect receptor binding. In one embodiment of the invention, L is selected from the group consisting of -NH-, -S-, -O-, -CO-, -CONH-, -CONHCH2-, -CH2CONH-, -CNHNH-, -CNHNHCH2-, -C=NOCH2-, -CH2NHCH2-, -CH2CH2NH-, -NHCH2CO-, -NHCH2CHOH-, -NHCNHNH-, -NHCONH-, cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1H-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2H-pyran, 2H-pyran, 4H-pyran, tetrahydrothiopyran, 3,4-dihydro-2H-thiopyran, 2H-thiin, 4H-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine. In another embodiment of the invention, Ar1 is selected from the group consisting of Ph, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, and Ar2 is selected from the group consisting of thiazoyl, furyl, pyranlyl, 2H-pyrrolyl, thienyl, pyrrolyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinoliziny, isoquinolyl, quinolyl, phthaliziny, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indoliziny, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl. Several hundred specific examples are individually prepd. and/or claimed. A variety of intermediates were also prepd. For instance, 5-methylpyrid-2-ylamidoxime was prepd. from 2-bromo-5-methylpyridine by Zn- and Pd-complex-mediated cyanation (56%) and reaction of the resulting nitrile with NH2OH.HCl (60%). Cyclization of the amidoxime with 3-cyanobenzoyl chloride (86%) gave invention compd. I. In a bioassay for **mGluR5** antagonism in primary astrocyte cultures from rats, the invention compds. had IC50 values in th range of 11 to 9140 nM.

ACCESSION NUMBER: 2002:676015 CAPLUS  
DOCUMENT NUMBER: 137:201315  
TITLE: Heteropolycyclic compounds, particularly pyridyl- and phenyl-substituted 1,2,4-oxadiazoles and analogs, and their use as metabotropic glutamate receptor antagonists for inhibiting neuronal damage  
INVENTOR(S): Slassi, Abdelmalik; Van Wagenen, Bradford; Stormann,

Thomas M.; Moe, Scott T.; Sheehan, Susan M.; McLeod,  
 Donald A.; Smith, Daryl L.; Isaac, Methvin Benjamin  
 PATENT ASSIGNEE(S): Can.  
 SOURCE: PCT Int. Appl., 272 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.    | KIND | DATE            | APPLICATION NO. | DATE     |
|---------------|------|-----------------|-----------------|----------|
| WO 2002068417 | A2   | <u>20020906</u> | WO 2002-US4689  | 20020219 |
| WO 2002068417 | A3   | 20021114        |                 |          |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
 CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,  
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-269847P P 20010221

AB The invention provides compds. and pharmaceutical compns. that act as **antagonists** at metabotropic glutamate receptors, and that are useful for treating neurol. diseases and disorders. Methods of prepg. the compds. also are disclosed. The compds. exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, notably **mGluR5**. In particular, medical conditions assocd. with metabotropic glutamate receptors and therefore targeted by the invention compds. include stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease. The invention provides methods of treating diseases assocd. with excitatory activation of an mGluR Group I receptor, and of **inhibiting** neuronal damage caused by excitatory activation of an mGluR Group I receptor, specifically wherein the mGluR Group I receptor is **mGluR5**. In one aspect of the invention, the **antagonists** may be represented by the general formula Ar1-L-Ar2, wherein Ar1 is an optionally substituted heteroarom. moiety, and Ar2 is an optionally substituted benzene ring. The L moiety is a group that not only covalently binds to the Ar1 and Ar2 moieties, and which facilitates adoption of the correct spatial orientation of Ar1 and Ar2, but also itself may interact with the protein, to effect receptor binding. In one embodiment of the invention, L is selected from the group consisting of -NH-, -S-, -O-, -CO-, -CONH-, -CONHCH2-, -CH2CONH-, -CNHNH-, -CNHNHCH2-, -C=NOCH2-, -CH2NHCH2-, -CH2CH2NH-, -NHCH2CO-, -NHCH2CHOH-, -NHCNHNH-, -NHCONH-, cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1H-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2H-pyran, 2H-pyran, 4H-pyran,

tetrahydrothiopyran, 3,4-dihydro-2H-thiopyran, 2H-thiin, 4H-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine. In another embodiment of the invention, Ar1 is selected from the group consisting of Ph, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, and Ar2 is selected from the group consisting of thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrrolyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinoliziny, isoquinolyl, quinolyl, phthaliziny, naphthyridinyl, quinazoliny, cinnoliny, isothiazolyl, quinoxaliny, indoliziny, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl. Several hundred specific examples are individually prepd. and/or claimed. A variety of intermediates were also prepd. For instance, 5-methylpyrid-2-ylamidoxime was prepd. from 2-bromo-5-methylpyridine by Zn- and Pd-complex-mediated cyanation (56%) and reaction of the resulting nitrile with NH<sub>2</sub>OH.HCl (60%). Cyclization of the amidoxime with 3-cyanobenzoyl chloride (86%) gave invention compd. I. In a bioassay for **mGluR5** antagonism in primary astrocyte cultures from rats, the invention compds. had IC<sub>50</sub> values in th range of 11 to 9140 nM.

- ST oxadiazole imidazole oxazole furan prepn **mGluR5**  
**antagonist**; heteropolycyclic phenylpyridyloxadiazole prepn  
 metabotropic glutamate receptor **antagonist** neuroprotectant
- IT Glutamate receptors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (metabotropic, **mGluR5**; prepn. of pyridyl- and  
 phenyl-substituted oxadiazoles and analogs as metabotropic glutamate  
 receptor **antagonists** for **inhibiting** neuronal  
 damage)
- IT Analgesics  
 Anti-Alzheimer's agents  
 Anti-ischemic agents  
 Anticonvulsants  
 Antimigraine agents  
 Antiparkinsonian agents  
**Anxiolytics**  
 Glutamate antagonists  
 Nervous system agents  
 Psychotropics  
 (prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as  
 metabotropic glutamate receptor antagonists for **inhibiting** neuronal  
 damage)
- IT Alzheimer's disease  
**Anxiety**  
 Epilepsy  
 Hypoglycemia  
 Hypoxia, animal  
 Mental disorder  
 Pain  
 Parkinson's disease  
 (treatment of; prepn. of pyridyl- and phenyl-substituted oxadiazoles  
 and analogs as metabotropic glutamate receptor antagonists for  
**inhibiting** neuronal damage)
- L1 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS
- AB The selective and systemically active **antagonist** for the  
 metabotropic glutamate receptor subtype 5 (**mGluR5**),  
 2-methyl-6-(phenylethynyl)pyridine (MPEP) was shown to display



**anxiolytic**-like activity in a no. of unconditioned assays of stress and **anxiety** (elevated plus maze, shock probe burying, marble burying, social interaction, and stress-induced hyperthermia) in rodents. In this report, we extend these observations found using unconditioned models of **anxiety** to include three models of conditioned **anxiety**, comparing the activity of MPEP to the clin. used **anxiolytics**, diazepam, and buspirone. MPEP and diazepam, but not buspirone, showed **anxiolytic**-like activity in the fear-potentiated startle (FPS) model. In a conditioned ultrasonic vocalization (USV) procedure, MPEP, diazepam, and buspirone reduced vocalizations to a similar degree. In the modified Geller-Seifter procedure, MPEP, diazepam, and buspirone displayed statistically significant **anxiolytic**-like activity, increasing the no. of punished responses. Thus, these findings confirm and extend previous reports that MPEP exhibits **anxiolytic**-like activity in rats, and suggests that development of **mGluR5 antagonists** may provide a novel approach to treating **anxiety** disorders.

ACCESSION NUMBER: 2002:512133 CAPLUS  
 TITLE: **Anxiolytic**-like activity of the **mGluR5 antagonist** MPEP. A comparison with diazepam and buspirone  
 AUTHOR(S): Brodtkin, Jesse; Busse, Chris; Sukoff, Stacey J.; Varney, Mark A.  
 CORPORATE SOURCE: Merck Research Laboratories, San Diego, CA, 92121, USA  
 SOURCE: Pharmacology, Biochemistry and Behavior (2002), 73(2), 359-366  
 CODEN: PBBHAU; ISSN: 0091-3057  
 PUBLISHER: Elsevier Science Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Anxiolytic**-like activity of the **mGluR5 antagonist** MPEP. A comparison with diazepam and buspirone  
 AB The selective and systemically active **antagonist** for the metabotropic glutamate receptor subtype 5 (**mGluR5**), 2-methyl-6-(phenylethynyl)pyridine (MPEP) was shown to display **anxiolytic**-like activity in a no. of unconditioned assays of stress and **anxiety** (elevated plus maze, shock probe burying, marble burying, social interaction, and stress-induced hyperthermia) in rodents. In this report, we extend these observations found using unconditioned models of **anxiety** to include three models of conditioned **anxiety**, comparing the activity of MPEP to the clin. used **anxiolytics**, diazepam, and buspirone. MPEP and diazepam, but not buspirone, showed **anxiolytic**-like activity in the fear-potentiated startle (FPS) model. In a conditioned ultrasonic vocalization (USV) procedure, MPEP, diazepam, and buspirone reduced vocalizations to a similar degree. In the modified Geller-Seifter procedure, MPEP, diazepam, and buspirone displayed statistically significant **anxiolytic**-like activity, increasing the no. of punished responses. Thus, these findings confirm and extend previous reports that MPEP exhibits **anxiolytic**-like activity in rats, and suggests that development of **mGluR5 antagonists** may provide a novel approach to treating **anxiety** disorders.

L1 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2003 ACS  
 AB Metabotropic glutamate receptors (mGluR) are a family of eight subtypes of G-protein coupled receptors. Recently, MPEP (2-methyl-6-

(phenylethynyl)pyridine) was described as a subtype selective, potent **mGluR5 antagonist**. In vitro, MPEP was shown to interact with an allosteric binding site located in the transmembrane domain, independently from the glutamate binding site located in the large N-terminal domain. In vivo, profiling of MPEP suggests a therapeutic potential for **mGluR5 antagonists** in anxiety related disorders, inflammatory pain and drug dependence. MPEP was originally identified by chem. derivatization of two leads identified by high capacity screening at the human mGlu5 receptor, SIB-1757 (6-methyl-2-(phenazo)pyridin-3-ol) and SIB-1893 ((E)-2-methyl-6-(phenylethenyl)pyridine). Here, we describe the lead optimization process which led to the identification of MPEP, as well as the SAR of this new class of **antagonists**. Examples will be given to illustrate the role of arom. substituents in the functional activity as well as in the binding affinity at the mGlu5 receptor.

ACCESSION NUMBER: 2002:190271 CAPLUS  
 TITLE: Structure activity relationships, receptor docking of phenylethynylpyridine derivatives, a series of selective non-competitive inhibitors of the mGlu5 receptor  
 AUTHOR(S): Gasparini, Fabrizio  
 CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, 4002 Basle, Switz.  
 SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), MEDI-152. American Chemical Society: Washington, D. C.  
 CODEN: 69CKQP  
 DOCUMENT TYPE: Conference; Meeting Abstract  
 LANGUAGE: English

AB Metabotropic glutamate receptors (mGluR) are a family of eight subtypes of G-protein coupled receptors. Recently, MPEP (2-methyl-6-(phenylethynyl)pyridine) was described as a subtype selective, potent **mGluR5 antagonist**. In vitro, MPEP was shown to interact with an allosteric binding site located in the transmembrane domain, independently from the glutamate binding site located in the large N-terminal domain. In vivo, profiling of MPEP suggests a therapeutic potential for **mGluR5 antagonists** in anxiety related disorders, inflammatory pain and drug dependence. MPEP was originally identified by chem. derivatization of two leads identified by high capacity screening at the human mGlu5 receptor, SIB-1757 (6-methyl-2-(phenazo)pyridin-3-ol) and SIB-1893 ((E)-2-methyl-6-(phenylethenyl)pyridine). Here, we describe the lead optimization process which led to the identification of MPEP, as well as the SAR of this new class of **antagonists**. Examples will be given to illustrate the role of arom. substituents in the functional activity as well as in the binding affinity at the mGlu5 receptor.

L1 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB Glutamate receptors play an essential role in fear-related learning and memory. The present study was designed to assess the role of the group I metabotropic glutamate receptor (mGluR) subtype 5 in the acquisition and retrieval of conditioned fear in rats. The selective **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)-pyridine (MPEP) was applied systemically (0.0, 0.3, 3.0, 30.0 mg/kg per os) 60 min before the acquisition training and before the expression of conditioned fear, resp., in the fear-potentiated startle paradigm. MPEP dose-dependently blocked the acquisition of fear. This effect was not due to state-dependent

learning. MPEP also prevented the expression of fear at a dose of 30.0 mg/kg. As a pos. control for these effects, the authors showed that the benzodiazepine **anxiolytic** compd. diazepam (1.25 mg/kg i.p.) also blocked acquisition and expression of fear potentiated startle. MPEP did not affect the baseline startle magnitude, short-term habituation of startle, sensitization of startle by footshocks or prepulse **inhibition** of startle. These data indicate a crucial role for **mGluR5** in the regulation of fear conditioning. In the highest dose MPEP might exert **anxiolytic** properties.

ACCESSION NUMBER: 2001:502705 CAPLUS  
 DOCUMENT NUMBER: 135:236855  
 TITLE: The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear conditioning in rats  
 AUTHOR(S): Schulz, B.; Fendt, M.; Gasparini, F.; Lingenhohl, K.; Kuhn, R.; Koch, M.  
 CORPORATE SOURCE: Animal Physiology, University of Tübingen, Tübingen, Germany  
 SOURCE: Neuropharmacology (2001), 41(1), 1-7  
 CODEN: NEPHBW; ISSN: 0028-3908  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Glutamate receptors play an essential role in fear-related learning and memory. The present study was designed to assess the role of the group I metabotropic glutamate receptor (mGluR) subtype 5 in the acquisition and retrieval of conditioned fear in rats. The selective **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)-pyridine (MPEP) was applied systemically (0.0, 0.3, 3.0, 30.0 mg/kg per os) 60 min before the acquisition training and before the expression of conditioned fear, resp., in the fear-potentiated startle paradigm. MPEP dose-dependently blocked the acquisition of fear. This effect was not due to state-dependent learning. MPEP also prevented the expression of fear at a dose of 30.0 mg/kg. As a pos. control for these effects, the authors showed that the benzodiazepine **anxiolytic** compd. diazepam (1.25 mg/kg i.p.) also blocked acquisition and expression of fear potentiated startle. MPEP did not affect the baseline startle magnitude, short-term habituation of startle, sensitization of startle by footshocks or prepulse **inhibition** of startle. These data indicate a crucial role for **mGluR5** in the regulation of fear conditioning. In the highest dose MPEP might exert **anxiolytic** properties.

IT **Anxiolytics**  
 Learning  
 (metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine MPEP blocks fear conditioning in rats)

IT Glutamate receptors  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (metabotropic, **mGluR5**; metabotropic glutamate receptor **antagonist** 2-methyl-6-(phenylethynyl)-pyridine MPEP blocks fear conditioning in rats)

L1 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB A review, with 28 refs. Although multiple metabotropic glutamate (mglu) receptor subtypes were cloned in the early 1990s, progress in the characterization of these receptors has been slow because of difficulties

in obtaining subtype-selective ligands. However, in the past few years exciting progress has been made on the mglu5 receptor subtype following the identification of selective non-amino-acid-like ligands that implicate the mglu5 receptor as a potentially important therapeutic target, particularly for the treatment of pain and **anxiety**.

ACCESSION NUMBER: 2001:467137 CAPLUS  
 DOCUMENT NUMBER: 135:221343  
 TITLE: Novel allosteric antagonists shed light on mglu5 receptors and CNS disorders  
 AUTHOR(S): Spooren, W. P. J. M.; Gasparini, F.; Salt, T. E.; Kuhn, R.  
 CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, CH-4002, Switz.  
 SOURCE: Trends in Pharmacological Sciences (2001), 22(7), 331-337  
 CODEN: TPHSDY; ISSN: 0165-6147  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English  
 REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review, with 28 refs. Although multiple metabotropic glutamate (mglu) receptor subtypes were cloned in the early 1990s, progress in the characterization of these receptors has been slow because of difficulties in obtaining subtype-selective ligands. However, in the past few years exciting progress has been made on the mglu5 receptor subtype following the identification of selective non-amino-acid-like ligands that implicate the mglu5 receptor as a potentially important therapeutic target, particularly for the treatment of pain and **anxiety**.

IT Analgesics

**Anxiolytics**

(allosteric antagonists shed light on mGlu5 receptors and CNS disorders)

IT Glutamate **antagonists**

(mGluR5; allosteric **antagonists** shed light on mGlu5 receptors and CNS disorders)

IT Glutamate receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(metabotropic, mGluR5; allosteric **antagonists** shed light on mGlu5 receptors and CNS disorders)

L1 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of mGluR5. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive mGluR5 **antagonist**. Studies using these agents have yielded data to support the involvement of mGluR5 in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for inhibition of quisqualate-stimulated

phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory pain. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

ACCESSION NUMBER: 2000:903884 CAPLUS  
DOCUMENT NUMBER: 135:13755  
TITLE: Methylphenylethynylpyridine (MPEP) (Novartis)  
AUTHOR(S): Micheli, Fabrizio  
CORPORATE SOURCE: Glaxo Wellcome Medicines Research Centre, Verona, 37135, Italy  
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2000) 1(3), 355-359  
CODEN: COIDAZ  
PUBLISHER: PharmaPress Ltd.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of mGluR5. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive mGluR5 **antagonist**. Studies using these agents have yielded data to support the involvement of mGluR5 in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory pain. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

IT Glutamate receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(AMPA-binding, antagonist; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Analgesics  
Anti-ischemic agents  
Anticonvulsants  
**Anxiolytics**  
(MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Glutamate antagonists  
(NMDA antagonists; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Glutamate receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)

09/821,416

(metabotropic, mGluR5, antagonist; MPEP in treatment of epilepsy, stroke, anxiety, pain, and neurodegenerative disease)

IT 96206-92-7, MPEP  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MPEP in treatment of epilepsy, stroke, anxiety, pain, and neurodegenerative disease)

L1 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS  
AB Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ACCESSION NUMBER: 2000:846141 CAPLUS  
DOCUMENT NUMBER: 134:36966  
TITLE: **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents  
AUTHOR(S): Spooren, Will P. J. M.; Vassout, Annick; Neijt, Hans C.; Kuhn, Rainer; Gasparini, Fabrizio; Roux, Silvain; Porsolt, Roger D.; Gentsch, Conrad  
CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, Switz.  
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 295(3), 1267-1275  
CODEN: JPETAB; ISSN: 0022-3565  
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT  
TI **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents  
AB Recently, selective and systemically active antagonists for the

metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ST methylphenylethynylpyridine **mGluR5 antagonist**  
**anxiolytic**

IT Behavior  
(locomotor; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT **Anxiolytics**  
Psychotomimetics  
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Glutamate receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (metabotropic, **mGluR5**; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Mental activity  
(sedation; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

L1 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB The invention provides the use of selective **mGluR5 antagonists** for the treatment of pain and **anxiety**, and the use of **mGluR antagonists** for the treatment of pain in which the analgesic effect is achieved by interaction of the **antagonists** primarily or predominantly at peripheral **mGluR** receptors.

09/821,416

ACCESSION NUMBER:  
DOCUMENT NUMBER:  
TITLE:

2000:240944 CAPLUS  
132:246378

**mGluR5 metabotropic glutamate receptor  
antagonists** for the treatment of pain and  
**anxiety**

INVENTOR(S):

Allgeier, Hans; Cosford, Nicholas David; Flor, Peter  
Josef; Gasparini, Fabrizio; Gentsch, Conrad; Hess,  
Stephen D.; Johnson, Edwin Carl; Kuhn, Rainer;  
Tricklebank, Mark; Urban, Laszlo; Varney, Mark Andrew;  
Velicelebi, Gonul; Walker, Katharine  
Novartis A.-G., Switz.; Novartis-Erfindungen  
Verwaltungsgesellschaft m.b.H.; Sibia Neurosciences  
Inc.

PATENT ASSIGNEE(S):

PCT Int. Appl., 21 pp.  
CODEN: PIXXD2

SOURCE:

DOCUMENT TYPE:

Patent  
English

LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2000020001          | A1   | 20000413 | WO 1999-EP7239  | 19990930   |
| W:                     | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |            |
| RW:                    | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |          |                 |            |
| CA 2345137             | AA   | 20000413 | CA 1999-2345137 | 19990930   |
| AU 9961984             | A1   | 20000426 | AU 1999-61984   | 19990930   |
| BR 9914215             | A  | 20010703 | BR 1999-14215   | 19990930   |
| EP 1117403             | A1   | 20010725 | EP 1999-948905  | 19990930   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO   |          |                 |            |
| JP 2002526408          | T2   | 20020820 | JP 2000-573360  | 19990930   |
| NO 2001001440          | A  | 20010515 | NO 2001-1440    | 20010321   |
| US 2001056084          | A1   | 20011227 | US 2001-821416  | 20010329   |
| PRIORITY APPLN. INFO.: |  |          | GB 1998-21503   | A 19981002 |
|                        |  |          | US 1998-220813  | A 19981223 |
|                        |  |          | WO 1999-EP7239  | W 19990930 |

OTHER SOURCE(S):  
REFERENCE COUNT:

MARPAT 132:246378  
9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **mGluR5 metabotropic glutamate receptor antagonists** for  
the treatment of pain and **anxiety**  
AB The invention provides the use of selective **mGluR5**  
**antagonists** for the treatment of pain and **anxiety**, and  
the use of **mGluR antagonists** for the treatment of pain in which  
the analgesic effect is achieved by interaction of the **antagonists**  
primarily or predominantly at peripheral **mGluR** receptors.  
ST **mGluR5 metabotropic glutamate receptor antagonist**  
pain; **anxiety mGluR5 metabotropic glutamate receptor**  
**antagonist**  
IT Nervous system

Delacroix



09/821,416

- (central; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)
- IT Inflammation
  - (inflammatory pain; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)
- IT Analgesics
  - Anxiolytics**
  - Biological transport
  - Blood-brain barrier
  - Drug delivery systems
    - (**mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)
- IT Glutamate receptors
  - RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
  - (metabotropic, **mGluR5**; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)
- IT Glutamate receptors
  - RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
  - (metabotropic, peripheral; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)
- IT Nerve, disease
  - (neuropathy, neuropathic pain; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)
- IT Drug delivery systems
  - (transdermal; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

=>

09/821,416

=> d his

(FILE 'HOME' ENTERED AT 21:37:18 ON 23 JAN 2003)

L1 FILE 'CAPLUS' ENTERED AT 21:37:27 ON 23 JAN 2003  
10 S MGLUR5(P) (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? O

L2 FILE 'REGISTRY' ENTERED AT 21:40:14 ON 23 JAN 2003  
STRUCTURE UPLOADED

FILE 'STNGUIDE' ENTERED AT 21:40:55 ON 23 JAN 2003

L3 FILE 'REGISTRY' ENTERED AT 21:42:48 ON 23 JAN 2003  
STRUCTURE UPLOADED

L4 2 S L3 SSS SAM

L5 17 S L3 SSS FULL

FILE 'CAPLUS' ENTERED AT 21:43:36 ON 23 JAN 2003

=> s 15

L6 14 L5

=> s 16 and (inhibit? or antagonist?) and (anxiety or anxious? or anxioly?)  
1540801 INHIBIT?

189529 ANTAGONIST?

9325 ANXIETY

395 ANXIOUS?

7715 ANXIOLY?

L7 0 L6 AND (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? OR  
ANXIOLY?)

=> s 16 and (anxiety or anxious? or anxioly?)

9325 ANXIETY

395 ANXIOUS?

7715 ANXIOLY?

L8 0 L6 AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)

=&gt; d 113 abs ibib kwic hitstr 1-2

L13 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5 antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory pain. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

ACCESSION NUMBER: 2000:903884 CAPLUS

DOCUMENT NUMBER: 135:13755

TITLE: Methylphenylethynylpyridine (MPEP) (Novartis)

AUTHOR(S): Micheli, Fabrizio

CORPORATE SOURCE: Glaxo Wellcome Medicines Research Centre, Verona, 37135, Italy

SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2000), 1(3), 355-359  
CODEN: COIDAZ

PUBLISHER: PharmaPress Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

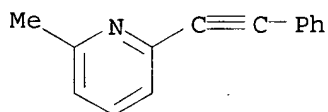
AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5 antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or. . .

IT Glutamate receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(AMPA-binding, antagonist; MPEP in treatment of epilepsy, stroke,

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**anxiety, pain, and neurodegenerative disease)**  
IT Analgesics  
Anti-ischemic agents  
Anticonvulsants  
**Anxiolytics**  
(MPEP in treatment of epilepsy, stroke, **anxiety, pain, and neurodegenerative disease)**  
IT Glutamate antagonists  
(NMDA antagonists; MPEP in treatment of epilepsy, stroke, **anxiety, pain, and neurodegenerative disease)**  
IT Glutamate receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (metabotropic, **mGluR5, antagonist**; MPEP in treatment of epilepsy, stroke, **anxiety, pain, and neurodegenerative disease)**  
IT **96206-92-7, MPEP**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MPEP in treatment of epilepsy, stroke, **anxiety, pain, and neurodegenerative disease)**  
IT **96206-92-7, MPEP**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MPEP in treatment of epilepsy, stroke, **anxiety, pain, and neurodegenerative disease)**  
RN 96206-92-7 CAPLUS  
CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

AB Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1,

10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ACCESSION NUMBER: 2000:846141 CAPLUS  
 DOCUMENT NUMBER: 134:36966  
 TITLE: **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents  
 AUTHOR(S): Spooren, Will P. J. M.; Vassout, Annick; Neijt, Hans C.; Kuhn, Rainer; Gasparini, Fabrizio; Roux, Silvain; Porsolt, Roger D.; Gentsch, Conrad  
 CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, Switz.  
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 295(3), 1267-1275  
 CODEN: JPETAB; ISSN: 0022-3565  
 PUBLISHER: American Society for Pharmacology and Experimental Therapeutics  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 TI **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents  
 AB . . . be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of. . . activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.  
 ST methylphenylethynylpyridine **mGluR5 antagonist**  
**anxiolytic**  
 IT Behavior  
 (locomotor; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)  
 IT **Anxiolytics**  
 Psychotomimetics  
 (**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)  
 IT Glutamate receptors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (metabotropic, **mGluR5**; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)  
 IT Mental activity  
 (sedation; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

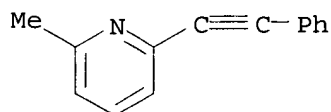
09/821,416

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

RN 96206-92-7 CAPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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